



# Cell and Tissue Based Biosensors

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Defense Science Office



# Biology at DARPA

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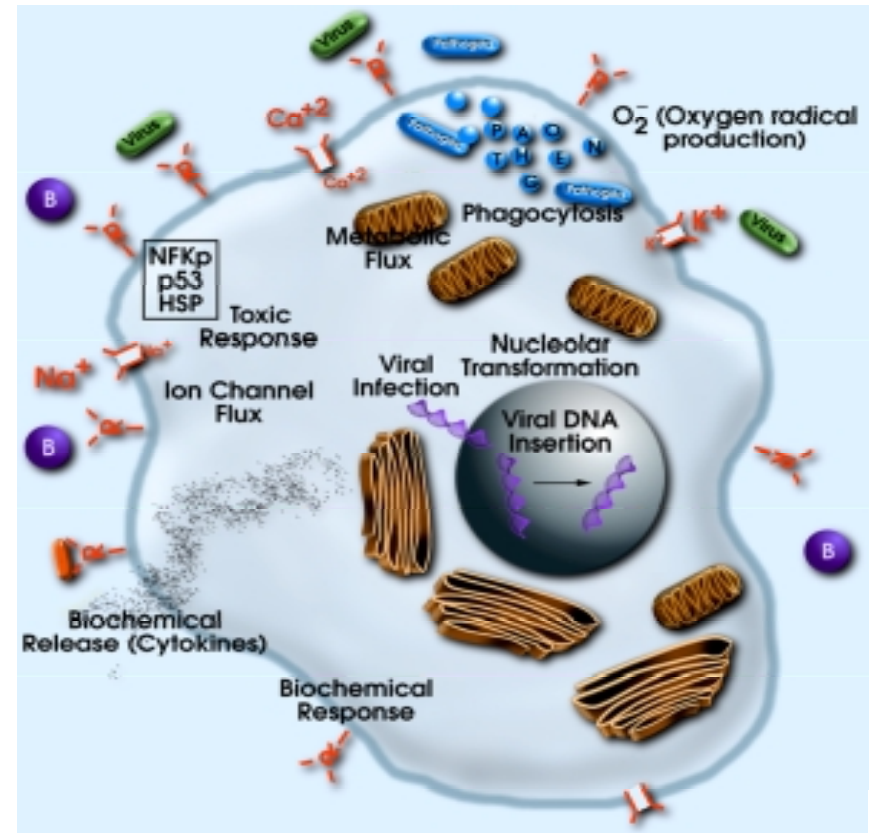
## Current Programs:

- Bioflips (Dr. Abe Lee, MTO, [aplee@darpa.mil](mailto:aplee@darpa.mil))
- Symbiosis (Dr. Anantha Krishnan, MTO, [akrishnan@darpa.mil](mailto:akrishnan@darpa.mil))
- Biocomputation (Dr. Sri Kumar, ITO, [skumar@darpa.mil](mailto:skumar@darpa.mil))
- Unconventional Pathogen Countermeasures (Dr. John Carney, DSO, [jcarney@darpa.mil](mailto:jcarney@darpa.mil))
- Bio-Info-Micro, (Dr. Eric Eisenstadt, DSO, [eeisenstadt@darpa.mil](mailto:eeisenstadt@darpa.mil))
- Biosurveillance (Dr. Murray Burke, ATO, [mburke@darpa.mil](mailto:mburke@darpa.mil))
- Tissue Based Biosensors (Dr. Alan S. Rudolph, DSO, [arudolph@darpa.mil](mailto:arudolph@darpa.mil))
- Controlled Biological and Biomimetic Systems (Dr. Alan S. Rudolph, DSO, [arudolph@darpa.mil](mailto:arudolph@darpa.mil))
- Advanced Diagnostics (Dr. Alan S. Rudolph, DSO, [arudolph@darpa.mil](mailto:arudolph@darpa.mil))
- Metabolic Engineering for Cellular Stasis (Dr. Robert Carnes, DSO, [arudolph@darpa.mil](mailto:arudolph@darpa.mil))

# Biological Cells As Sensors

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- Cell is unit machine in biology responsible for systems level processing
  - communicative
  - regenerative and progenic
  - self-powering/mobile
- Cells respond to environment in specific, reproducible and redundant ways
  - oxygen/nitrogen radicals
  - biochemical markers - cytokines/growth factors
  - morphological/structural
  - genetic
- Cell sensors do not require specific identification of threat
  - processing will result in identification
  - amplification of response



- **Response is predictive of functional consequences**
  - pathogenesis
  - human health risk



# Living Sensors: The Need

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- The list of possible environmental threats is growing
- Emerging threats and yet identified threats are increasing due to widening access to biotechnology
- Operational need for 'broad based' detection
  - 'canary on a chip'
  - "is it a safe environment?", "is there a change in the diagnostic test from a control sample?"
- Broad based detection will often require confirmatory testing ('trigger')



# What are Activity Detection Systems?

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- Detection systems based on response of biological cellular or tissue processor
- Respond to *known or unknown chem-bio threats*
- Provide three levels of information
  - Detection – state change in sample from good to bad
  - Classification – define threat into categories: bacterial, viral, toxin, combustion product
  - Identification – compare activity response to library of known responses and report activity probability match

# The Challenge

GOAL

To develop an activity based detection system using cells and tissues

How?

## Sample Collection & Preparation

- Sample Introduction
- Sample Types
- Sample Size
- Background Interferents

## Design & Engineering

- Optimal Cell Types
- Fluidics
- Adhesion
- Stability
- Optics

## Detection Capabilities

- Signatures of cell responses
  - Model & Simulants
  - BW & CW Agents
  - Unknown
  - Live vs. Dead
- Sensitivity
- Specificity
- Speed
- Dose/Response

## Data Acquisition & Data Analysis

- Modeling Single and Multi Cellular Arrays
- Signal Processing
  - Extraction of Signatures
- Decision Algorithms

# The General Setting for Computational Designs

**CONCEPT EXPLORATION  
PHASE**

**HYPOTHESIS TESTING**

**CONCEPT SELECTION**

**HYPOTHESIS TESTING**

**ESTIMATION**

**DEMONSTRATION/VALID  
ATION**

**ESTIMATION**

**FULL SCALE  
DEVELOPMENT**

**PROCESS CONTROL: TIME SERIES**

**PRODUCTION PHASE**

**PROCESS CONTROL: TIME SERIES**

**OPERATION AND  
SUPPORT**

# The General Setting for Developing A Cell Sensor



CONCEPT EXPLORATION  
PHASE

CONCEPT SELECTION

DEMONSTRATION/VALID  
ATION

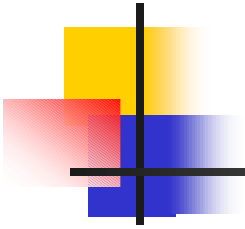
FULL SCALE  
DEVELOPMENT

***CALIBRATION***

PRODUCTION PHASE

OPERATION AND  
SUPPORT

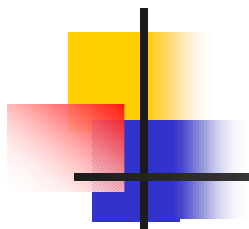




# Why Calibrate?

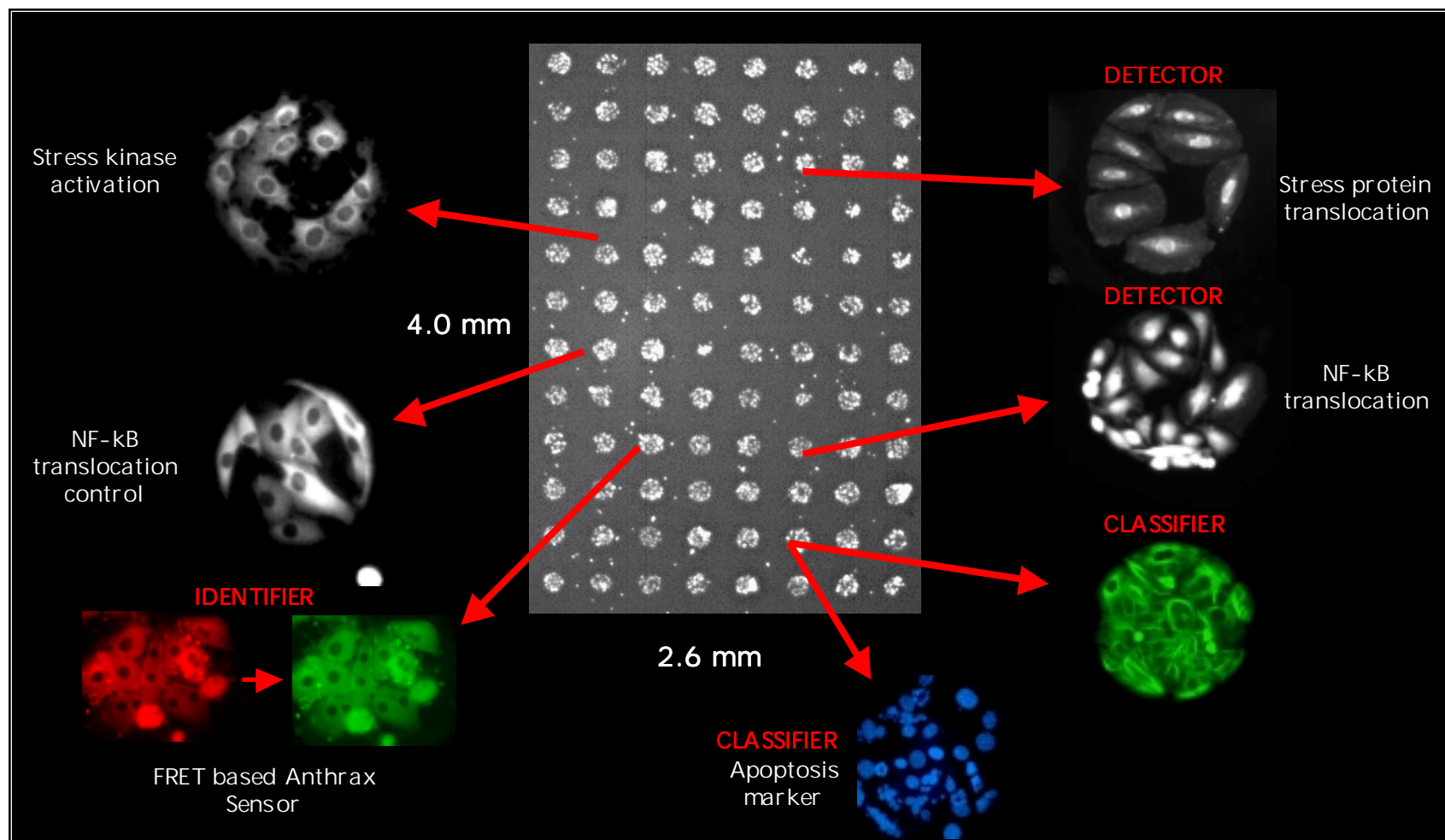
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- **If You Cannot Calibrate Your Phenomenon, It May Never Be Part Of An Device or Instrument-a Biosensor- or a ‘technology’**
- **There Is No Magic To Calibration: It Must Be Done Whether You Are Using Dose-response Curve Methods, Neural Nets, Mixture Models, Automatic Pattern Recognition or other computational tools.**



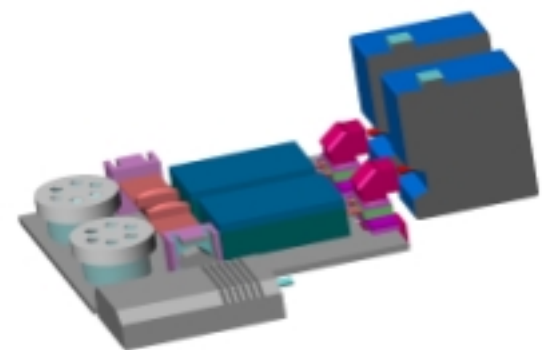
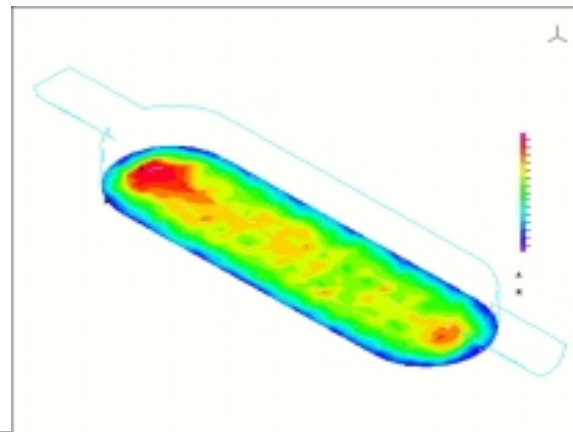
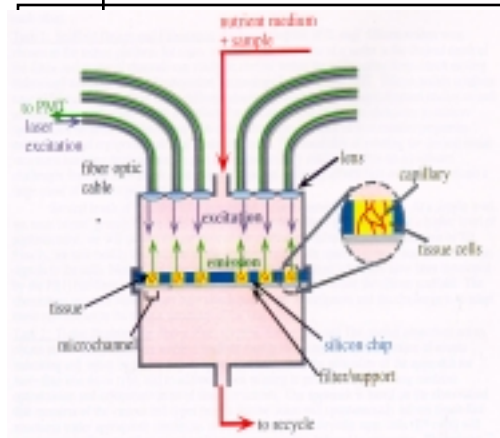
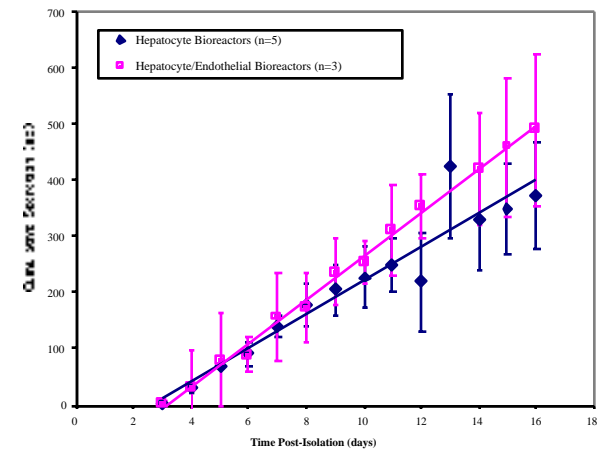
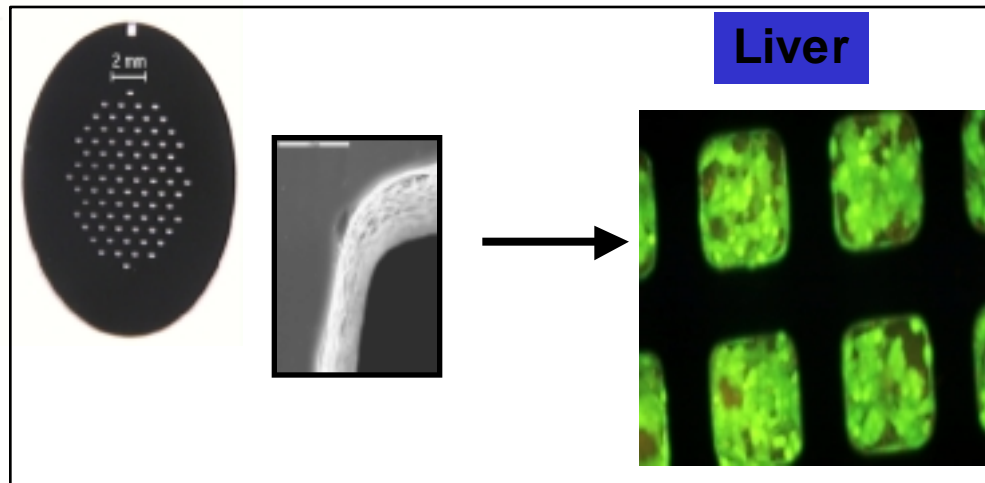
# Optical Cellular Microarrays

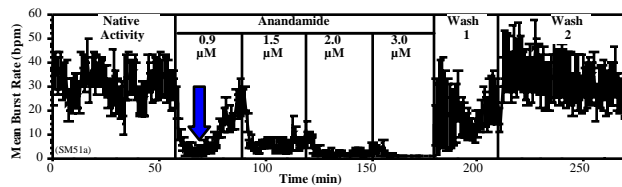
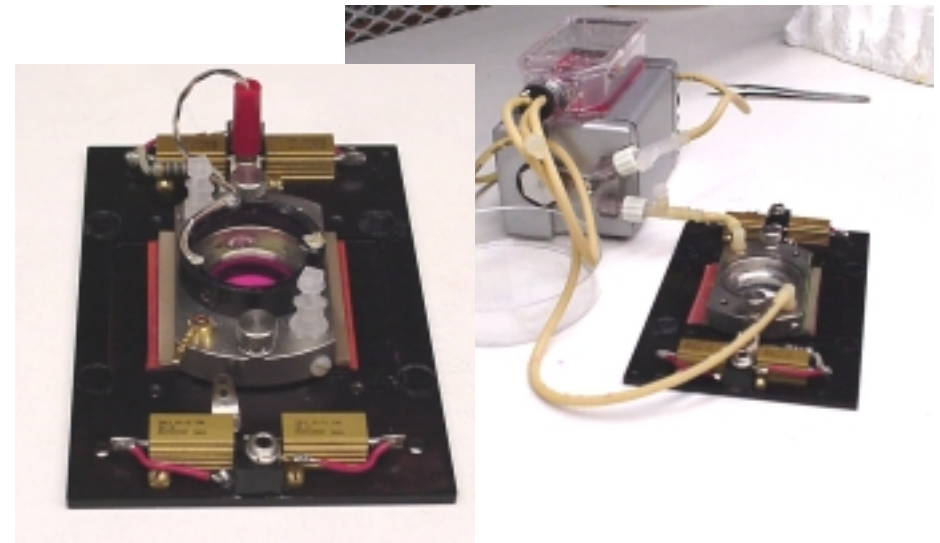
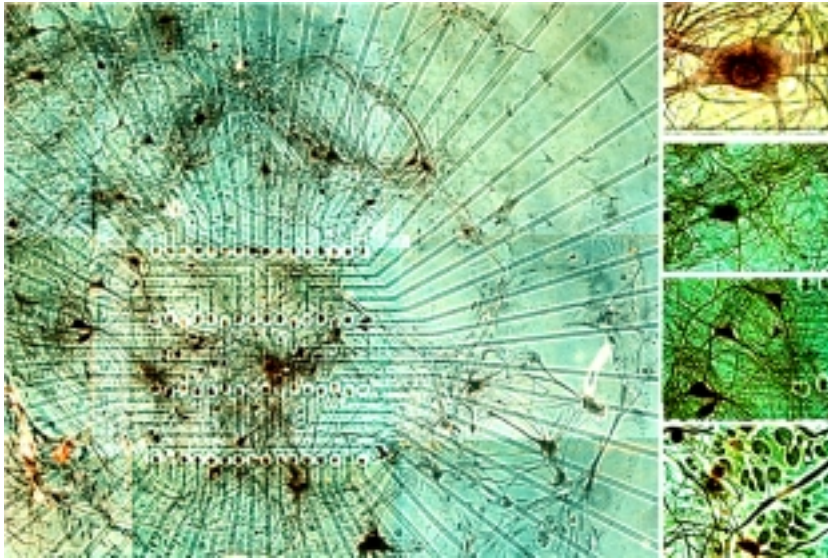
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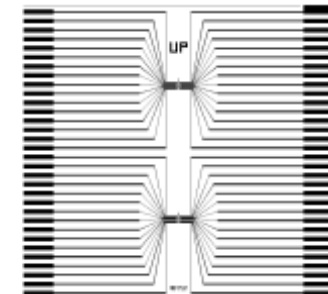
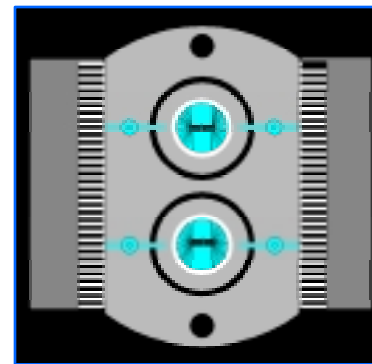
# Ex Vivo Tissue Engineered Toward "Human on a Chip"

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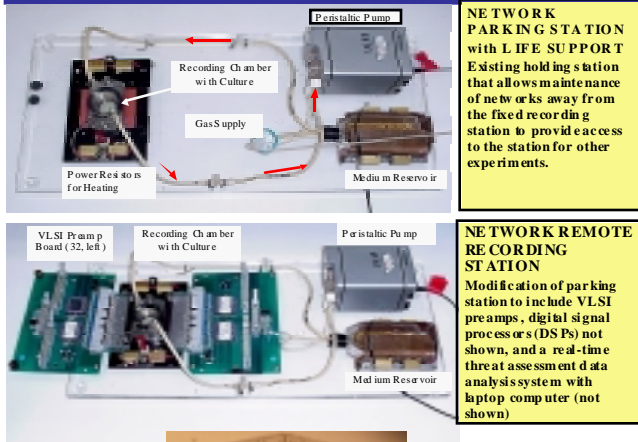


Box	BM solar	BM SD	B-AMTIE SD	B-AMTIE %MEN	B-ORION SD	B-ORION %MEN	B-PRD SD	B-PRD %MEN	B-ORION-SD SD	B-ORION-SD %MEN	B-AREA SD	B-AREA %MEN
-367	-50	15	-607	0.9	-354	0.97	397.5	70.9	8552	0.7	0.0	0.0
-342	-63	38	1900	0.9	-1000	1.4	-10.0	15	1000	0.7	1000	1000
-200	-52	17	586	0.6	505	3.8	55.0	1105	6912	0.8	0.0	0.0
-367	-53	0.9	30.9	0.12	382	2.90	13.0	24.9	1723	0.4	0.0	0.0
-130	-20	-49	1000	3.4	-1000	1.3	-10.0	13	1000	3.4	1000	1000
-318	-65	15	-436	0.7	-172	361	140.0	275	8610	0.4	3.0	3.0
-304	-53	15	-415	0.6	-50	344	170.5	294	8312	0.8	0.0	0.0
-377	-52	15	524	0.6	712	23.0	14	264	8610	0.3	5.0	5.0
-375	-54	13	-423	0.7	-329	812	66.3	119	3257	0.9	0.0	0.0
-40	-49	15	-445	0.3	-388	80.3	13.1	955.7	0.8	0.4	0.4	0.4
-256	-45	16	594	0.7	-383	360	178.2	324	2339	1.0	3.0	3.0
-374	-59	0.9	35.2	0.7	276	684	370.7	698	8028	0.2	1.6	1.6
key	-1SD	(R-50%)	MIN		-1SD	(R-5%)	MIN		-1SD	(R-75%)	MIN	



# Cell/Tissue Prototypes

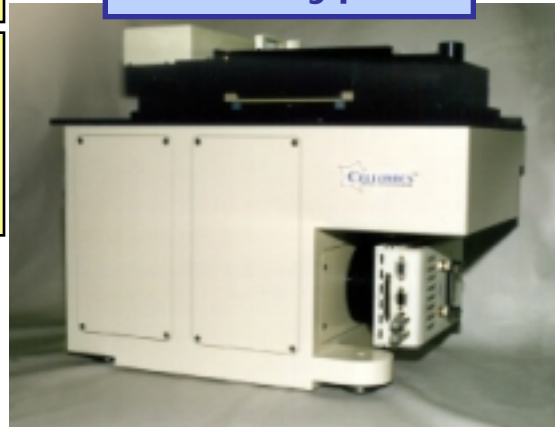
## Tissue Based Prototypes



## Interfaces & Fluidics



## Bench top Prototypes



## Mobile Systems



## Handheld Sensors

- *Testing and validation in progress*





# Summary

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- Intracellular computation and iterative experimental validation are critical to realizing a Defense capability using cells
- Calibration is essential toward technology development for sensors/diagnostics/therapeutics
- Encourage BIOCOMP investigators to collaborate with other biology programs at DARPA